REMARKS

Claims 93, 112, 113, and 115 –135 are pending.

Claims 93 and 112 have been rewritten in independent form. This amendment addresses the objection to claims 112 and 113 as being in improper dependent form.

Cancellation of claims 46, 48-49, 52, 54, 57, 90, 91, 92, 94-111, and 114 renders the rejections against those claims moot. New claims 115- 135 are supported throughout the specification. See, e.g., Table I, Figure 2, page 11, lines 29-33; page 14, lines 5-6; page 15, lines 19-23; page 18, lines 14-17. Further support for these claims is discussed below.

No new matter is added by this amendment.

Claim Rejections – 35 USC §112

Claims 93, 112 and 113 are rejected under 35 USC 112, first paragraph, as not being enabling and for lacking written description.

The examiner admits that the specification is enabling for a method for reducing the susceptibility of tropoelastin to thrombin, kallikrein, trypsin, plasmin, gelatinase B, or serum by mutating the sequences described in the specification, including Table 1. The examiner further states that the specification supports replacing arginine at position 515 with alanine (Claim 93). The examiner further states that for claims 112 and 113, a mutation at ALAAA sequences, which occurs at positions 593-597, is supported in the specification.

Claims 93 and 112 have been rewritten in independent form and are believed to overcome this rejection.

New claim 115 refers to a method of reducing the susceptibility of tropoelastin to proteolysis by thrombin, kallikrein or serum, comprising mutating one or more of the amino acid residues of the amino acid sequence RAAAG, so that the susceptiblity of the tropoelastin molecule to cleavage by thrombin, kallikrein or serum protease is reduced. This claim is

supported on page 12, line 30 to page 13, line 10 of the specification, which provides a list of the amino acid sequences which represent the portion of the tropoelastin molecule corresponding to position 507 to 523 of SEQ ID NO: 4 from human, rat, mouse and bovine sources. As can be seen from page 12, line 30 to page 13, line 10, the amino acid sequences RAAAG is completely conserved between these species. Moreover, the specification states at page 13, lines 12 to 16:

> "the subsequences identified in Table 1 are highly homologous with non human tropoelastin or elastin sequences, supporting the proposition that taking account of sequence differences the methods of the invention can be applied to different tropoelastin species".

Thus, the specification provides clear support that susceptibility to proteolysis by thrombin, kallikrein or serum can be reduced by mutating one or more amino acids of the sequences RAAAG of tropoelastin from many different species. Based on the information in the specification, there would be no undue burden of experimentation required in order to reduce the susceptibility to proteolysis by thrombin, kallikrein or serum in tropoelastin molecules.

> The Examiner considers that although making a mutation in the serine protease recognition sequence RAAAGLG might reduce susceptibility of tropoelastin to thrombin and kallikrein cleavage at that site, the Examiner considers that it would not reduce overall susceptibility of tropoelastin to thrombin and kallikrein cleavage because these enzymes recognize more than one sequence.

However, while there are multiple thrombin and kallikrein cleavage sites in the tropoelastin molecule, by eliminating one site that is susceptible to protease attack, overall susceptibility of the molecule to protease cleavage is reduced. Referring to Table 1 on page 63, by mutating one or more of the amino acid residues of the sequence RAAAG, 1 out of 3 thrombin susceptible sites is eliminated and one out of three susceptible sites is eliminated. The overall effect is a one-third reduction in sites susceptible to thrombin and kallikrein and thus a reduction in susceptibility to both thrombin and kallikrein. Accordingly, by mutating one or more of the amino acids of the sequence RAAAG, the susceptibility of tropoelastin to cleavage by thrombin is reduced.

> The Examiner considers that the claims do not comply with the written description requirement because the Examiner considers there is no support in the specification for making mutations specifically at one or more residues within the ranges specified in the current claims. We further note that the Examiner considers there is only support in the specification for replacing arginine with alanine.
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> However, the specification states:
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> "Alteration to reduce susceptibility to protease attack can be considered to involve removal or modification of the recognition site. An example of this modification is the replacement of lysine or arginine by an amino acid residue that is not positively charged. An example of this approach is the use of leucine to replace arginine in the sequence R/AAAGLG of Table 1 using common methods of mutagenesis such as those available commercially in the kit form."

Accordingly, the specification clearly discloses that arginine may be replaced with an amino acid residue that is not positively charged. Amino acids that are not positively charged have been well-known in the art for many years prior to the priority date of the present application. In support of this assertion, attached is an extract from a well-known biochemistry text (Stryeer, (1981), Biochemistry (W.H. Freeman and Company, San Francisco) which indicates at page 15 that lysine (K), arginine (R) are positively charged amino acids at neutral pH, while the amino acids serine (S), threonine (T), proline (P), glycine (G), alanine (A), valine (V), leucine (L), isoleucine (I), phenylalanine (F), tyrosine (Y), tryptophan (W), aspartate (D), glutamate (E), asparagine (N), glutamine (Q), cysteine (C), and methionine (M) are either uncharged or negatively charged at physiological pH. Accordingly, the specification discloses that arginine in the sequence RAAAG (or any other sequence that is susceptible to protease cleavage) can be replaced with any of the amino acids S, T, P, G, A, V, L, I, F, Y, W, D, E, N, Q, C or M.

Moreover, the procedural steps required to reduce the susceptibility of tropoelastin to proteolysis by a serine protease selected from a group consisting of thrombin, kallikrein, and serine protease would be clear to a person skilled in the art in light of the information in the specification. The inventor has identified, and it is clearly described in the specification, amino

acid sequences of tropoelastin which render tropoelastin susceptible to proteolysis by thrombin, kallikrein, serum, plasmin, trypsin, and gelatinase B (see Table 1). The specification clearly discloses that mutating these amino acid sequences will reduce or eliminate the susceptibility of the tropoelastin molecule to these enzymes. Moreover, the specification clearly indicates the types of mutations that would be required in order to achieve the invention as claimed. All that is required from a person skilled in the art is to mutate the amino acid sequence referred to in the claim.

Methods for mutagenesis of DNA sequence to alter an amino acid subsequence are well know to a person skilled in the art at the priority date of the application and, as indicated in the specification at page 14, lines 7 to 8, kits for mutagenesis were commercially available. Accordingly, it would have been a matter of routine in light of what is disclosed in the specification for a person skilled in the art to mutagenize tropoelastin sequence to obtain tropoelastin molecules having reduced or no susceptibility to proteolysis by thrombin, kallikrein and serine protease.

The sequence RAAAG occurs only once in the tropoelastin molecule (for example, at position 515 to 519 of SEQ ID NO:4). Accordingly, in order to carry out the method as defined in claim 1, in light of the information provided in the specification, it would be a straightforward and routine matter to mutate one or more amino acids in the sequence RAAAG. In this regard, the specification provides the human tropoelastin full-length DNA sequence (Figure 2), and in addition provides the relevant amino acid sequence from other species (page 12 and 13) as well as the sources from which sequences from other species may be obtained (page 12, first paragraph). Accordingly, the person skilled in the art is provided with all the necessary information in order to mutate the amino acid sequence RAAAG in tropoelastin.

Similarly, in light of the information provided in the specification, it would have been a matter of routine for a person skilled in the art to mutate other amino acid sequences referred to in the claims (SEQ ID NO: 8, 10, 11, 12, 13, 14, 15 and 16).

We submit that not only would there be no undue burden of experimentation placed on the person skilled in the art to carry out the methods as claimed in light of the information

provided in the specification, but that the specification clearly describes the invention is a way which conveys to one skilled in the art that the inventor had possession of the invention as claimed at the time of filing the application.

Reconsideration and withdrawal of the rejection is requested.

The Director of the U. S. Patent and Trademark Office is hereby authorized to charge any deficiency in any fees due with the filing of this paper to Deposit Account No. 08-3040.

Respectfully submitted,
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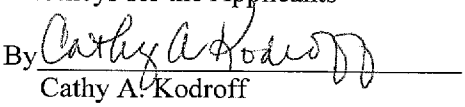
By 

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